Elevated serum glial fibrillary acidic protein (sGFAP) is associated with increased risk of neuromyelitis optica spectrum disorder attacks in the N-MOmentum randomised, masked, placebo-controlled clinical trial of inebilizumab

P1609

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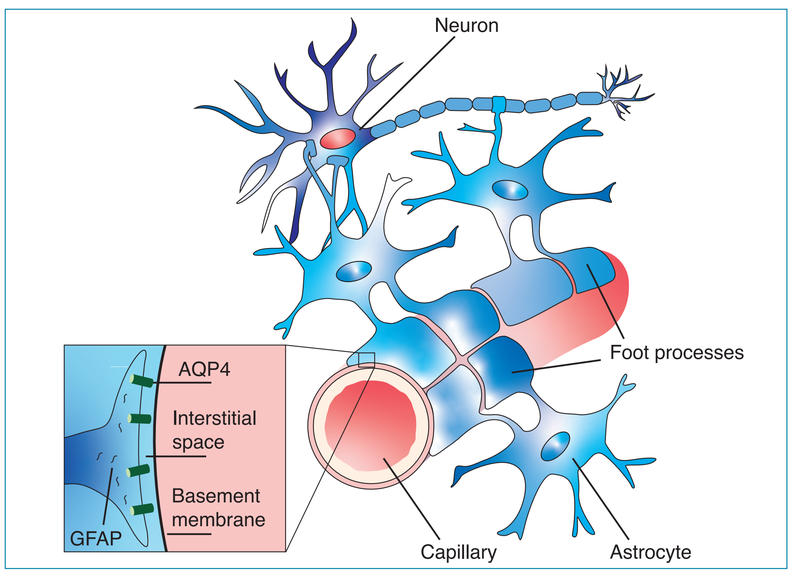
INTRODUCTION

- Neuromyelitis optica spectrum disorder (NMOSD) is a severe autoimmune disease that is characterized by recurrent inflammation of the optic nerve, spinal cord, brain or brainstem.[1,2]
- In patients with NMOSD, aquaporin-4, a water channel protein that is expressed on astrocytes, is frequently targeted by autoantibodies, which causes the selective destruction of astrocytes (**Figure 1**).[1]
- This results in increased concentration of glial fibrillary acidic protein (GFAP), an intermediate filament protein predominantly expressed by astrocytes, in serum and cerebrospinal fluid.[1]
- N-MOmentum was a randomized, placebo-controlled, double-masked trial of inebilizumab, an anti-CD19 monoclonal B-cell-depleting antibody, in patients with NMOSD.[3]
  - Baseline demographics and characteristics were generally similar between treatment groups.
  - Inebilizumab reduced the risk of NMOSD attacks by 73% compared with placebo; hazard ratio 0.272 (95% confidence interval [CI]: 0.150–0.496; $p < 0.0001$).[3]

Figure 1. sGFAP is a serum biomarker of astrocyte death.



GFAP is an intermediate filament protein predominantly expressed by astrocytes that is present in the serum and cerebrospinal fluid following astrocyte destruction.
AQP4, aquaporin-4; GFAP, glial fibrillary acidic protein; sGFAP, serum glial fibrillary acidic protein.

OBJECTIVES

- To investigate the relationship between prospectively sampled serum GFAP (sGFAP) concentration and disease activity in N-MOmentum clinical trial participants.

METHODS

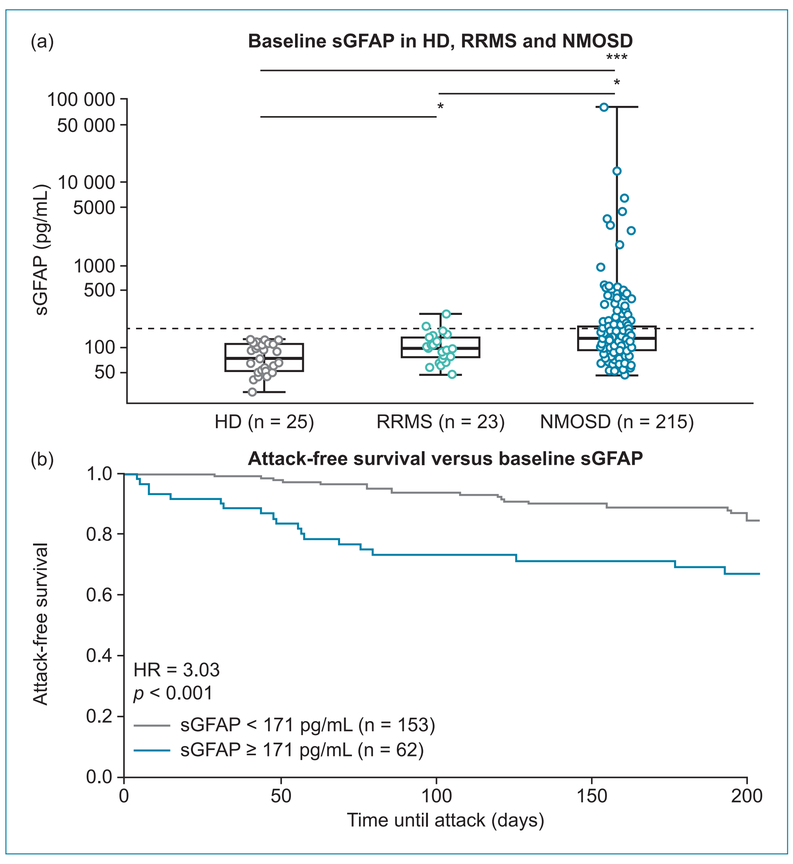
- sGFAP concentration was measured using the Quanterix Simoa GFAP assay in 1260 serial and attack-related samples collected from N-MOmentum study participants (n = 215) and from participants in two reference cohorts: healthy donors (HDs; n = 25) and patients with relapsing-remitting multiple sclerosis (RRMS; n = 23).
- Attacks during the 28-week randomized controlled period (RCP) were evaluated by the study investigators and by an independent adjudication committee using predefined attack criteria.[3]

RESULTS

Patients with NMOSD had higher sGFAP concentration than participants in reference cohorts

- Median sGFAP concentration was elevated in patients with NMOSD compared with the concentration in participants in the two reference cohorts (**Figure 2a**).
  - HDs = 73.3 pg/mL (interquartile range [IQR], 52.1, 108.7)
  - RRMS = 97.5 pg/mL (IQR, 76.5, 131.4)
  - NMOSD = 128.3 pg/mL (IQR, 92.0, 181.2).
- At baseline, elevated sGFAP concentration (defined as ≥ 3 standard deviations [SD] above HD mean [≥ 171 pg/mL]) was observed in 29% (62/215, $p < 0.001$) of NMOSD study participants and in 9% (2/23, $p < 0.05$) of patients in the RRMS reference cohort (**Figure 2a**).

Figure 2. Baseline sGFAP concentration and risk of adjudicated NMOSD attack in the RCP.



(a) sGFAP concentration in HD, RRMS and NMOSD. Dashed line represents 3 standard deviations from the HD mean (171 pg/mL; 29% of patients with NMOSD above HD mean). Box and whiskers represent sample quartiles. Statistical significance of differences in sGFAP concentration between groups was assessed using the Mann–Whitney U test (*$p < 0.05$, ***$p < 0.001$). (b) Kaplan–Meier plot of time until first NMOSD attack in all patients with baseline sGFAP concentration ≥ 171 pg/mL (3 SDs from HD mean) versus those with baseline sGFAP concentration < 171 pg/mL. The statistical significance of difference in time until first adjudicated attack between groups was assessed using Wald's test.
HD, healthy donor; HR, hazard ratio; NMOSD, neuromyelitis optica spectrum disorder; RRMS, relapsing-remitting multiple sclerosis; SD, standard deviation; sGFAP, serum glial fibrillary acidic protein.

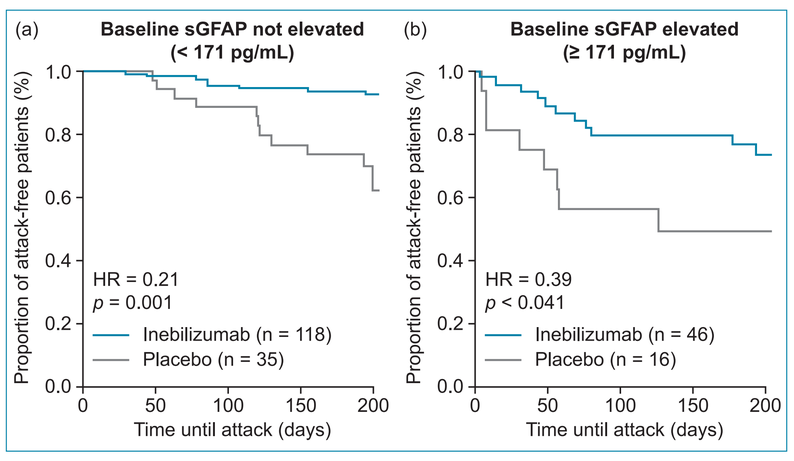
Patients with increased baseline sGFAP concentration were at an increased risk of an adjudicated NMOSD attack

- NMOSD study participants with elevated baseline sGFAP concentration were three times more likely to experience an adjudicated NMOSD attack than those with lower sGFAP concentration during the RCP ($p < 0.001$; **Figure 2b**).

Inebilizumab treatment was associated with decreased risk of adjudicated attack in patients with either normal or elevated baseline sGFAP concentration

- In patients with normal baseline sGFAP concentration, inebilizumab reduced the risk of an adjudicated attack by 79% compared with patients receiving placebo: hazard ratio 0.21, $p < 0.001$ (**Figure 3a**).
- In patients with elevated baseline sGFAP concentration, inebilizumab reduced the risk of an adjudicated attack by 61% compared with patients receiving placebo: hazard ratio 0.39, $p = 0.041$ (**Figure 3b**).

Figure 3. Attack-free survival in patients receiving inebilizumab or placebo with or without baseline elevation of sGFAP concentration.

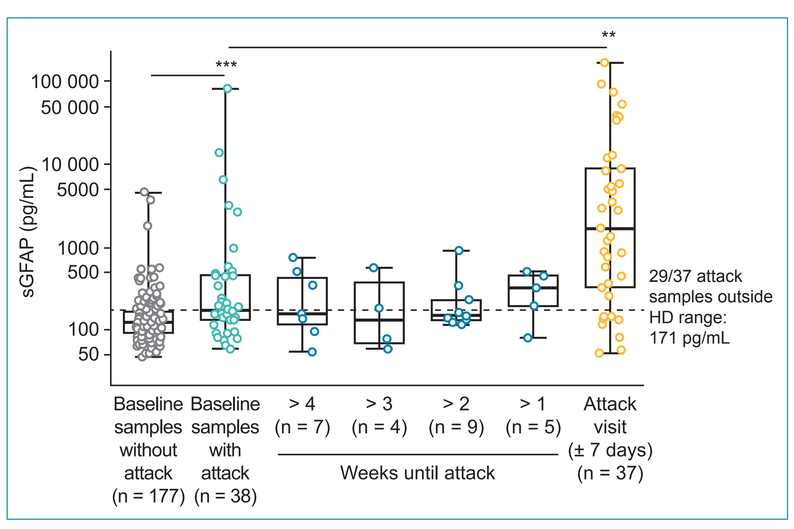


(a) Kaplan–Meier plot of time until first attack between patients receiving inebilizumab or placebo with sGFAP concentration < 171 pg/mL and (b) sGFAP concentration ≥ 171 pg/mL. The statistical significance of difference in time until first attack between groups was assessed using Wald's test.
HR, hazard ratio; sGFAP, serum glial fibrillary acidic protein.

sGFAP levels increased during adjudicated NMOSD attacks

- Concentration of sGFAP increased within 1 week of an adjudicated NMOSD attack during the RCP. Attack samples could have been drawn before or after an attack (**Figure 4**).

Figure 4. sGFAP concentration from baseline and leading to an adjudicated NMOSD attack.

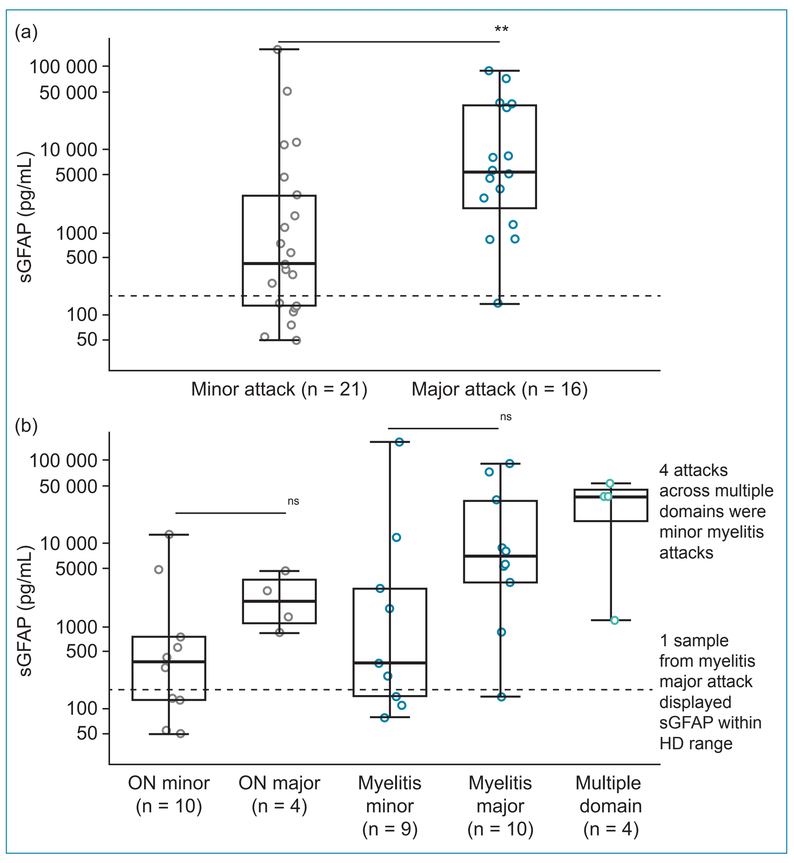


**$p < 0.01$, ***$p < 0.001$.
Baseline sGFAP concentration split by those who did not have an adjudicated attack during the RCP (n = 177) and those that did have an attack later in the RCP (n = 38), along with sGFAP at > 4 weeks (n = 7), > 3 weeks (n = 4), > 2 weeks (n = 9), > 1 week (n = 5), and at the closest visit within 1 week of an adjudicated NMOSD attack (n = 37). The statistical significance of the sGFAP level differences between baseline samples was assessed using the Mann–Whitney U test. The statistical significance of change in sGFAP concentration from baseline to an attack was assessed using the Wilcoxon signed-rank test.
HD, healthy donor; NMOSD, neuromyelitis optica spectrum disorder; RCP, randomized controlled period; sGFAP, serum glial fibrillary acidic protein.

Elevated sGFAP concentration was associated with increased adjudicated NMOSD attack severity

- sGFAP concentration was significantly higher in patients who had major adjudicated attacks than in those who had minor adjudicated attacks ($p < 0.01$; **Figure 5a**).
- Concentrations of sGFAP trended higher in major versus minor adjudicated attacks across all organ domains, including attacks that only affected the optic nerve (**Figure 5b**).

Figure 5. sGFAP concentration and adjudicated NMOSD attack severity, as measured by the OSIS.[4]

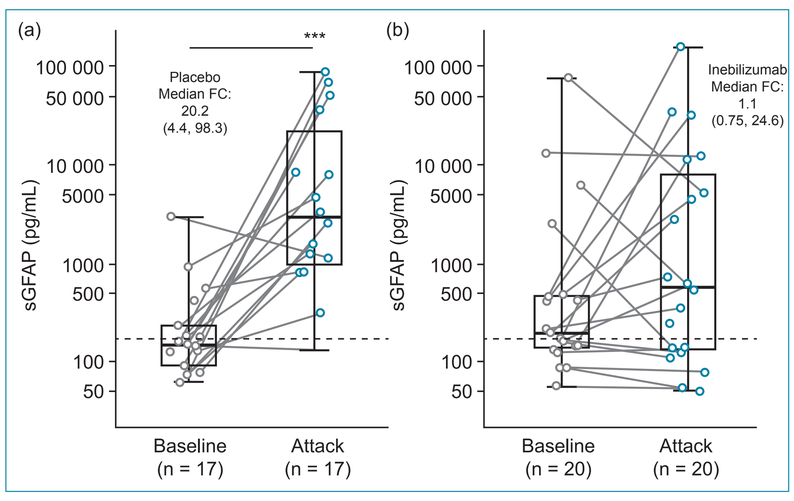


**$p < 0.01$.
sGFAP concentration within 1 week of adjudicated NMOSD attack split by (a) attack severity and (b) organ domain involvement as measured by the OSIS. Box and whiskers represent sample quantiles. Significance between groups was assessed using Mann–Whitney U test. For characterization of attacks in N-MOmentum by severity, please see poster 358.
HD, healthy donor; NMOSD, neuromyelitis optica spectrum disorder; ns, not significant; ON, optic neuritis; OSIS, optico-spinal impairment score; sGFAP, serum glial fibrillary acidic protein.

sGFAP concentrations during adjudicated NMOSD attacks were lower in inebilizumab-treated patients than in those receiving placebo

- sGFAP concentration increased during adjudicated NMOSD attacks, but concentration was lower in patients who received inebilizumab than in those who received placebo ($p = 0.048$; **Figure 6**).
  - sGFAP concentration increased within 1 week following an adjudicated NMOSD attack during the RCP in study participants who received placebo (median fold change [IQR]: 20.2 (4.4, 98.3; n = 17 attacks; $p = 0.001$).
  - sGFAP concentration increased nominally but not significantly during adjudicated attacks in inebilizumab-treated patients (median fold change (IQR): 1.1 (0.75, 24.6; n = 20 attacks; p = not significant).
- Seven inebilizumab samples and one placebo sample were within the HD range during adjudicated attacks; $p = 0.048$.

Figure 6. sGFAP concentration during adjudicated NMOSD attacks by treatment group.

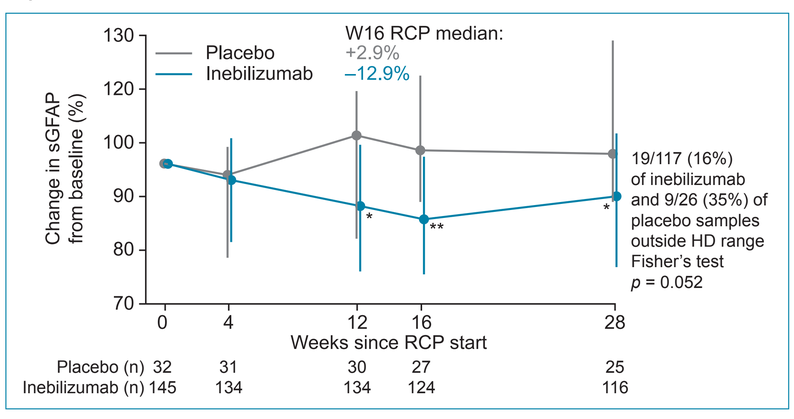


***$p < 0.001$.
sGFAP concentration in patients who received (a) placebo and (b) inebilizumab during adjudicated attacks. The significance of increases from baseline was assessed using the Wilcoxon signed-rank test.
FC, fold change; HD, healthy donor; NMOSD, neuromyelitis optica spectrum disorder; sGFAP, serum glial fibrillary acidic protein.

sGFAP concentration decreased from baseline in inebilizumab-treated patients who did not experience an adjudicated NMOSD attack

- Of 143 study participants who did not have an adjudicated NMOSD attack, GFAP decreased after inebilizumab treatment and fewer inebilizumab-treated participants had elevated sGFAP concentration (sGFAP ≥ 171 pg/mL) at the end of the RCP than those receiving placebo (16% [19/117] versus 35% [9/26]; $p = 0.052$; **Figure 7**).

Figure 7. sGFAP during the RCP in patients who did not experience an adjudicated NMOSD attack.



*$p < 0.05$, **$p < 0.01$.
Error bars represent interquartile range. Significance of percentage change in baseline was assessed using the Mann–Whitney U test.
HD, healthy donor; RCP, randomized controlled periods; sGFAP, serum glial fibrillary acidic protein.

CONCLUSIONS

- In the N-MOmentum study, inebilizumab treatment was associated with a decreased risk of an adjudicated NMOSD attack, compared with placebo, in patients with normal or elevated sGFAP concentrations at baseline.
- Participants with NMOSD had increased sGFAP concentration compared with participants in the HD and the RRMS reference cohorts.
- sGFAP concentration increased significantly within 1 week of an adjudicated attack and correlated with adjudicated NMOSD attack severity.
- sGFAP concentrations during adjudicated NMOSD attacks were lower in inebilizumab-treated patients than in participants receiving placebo.
  - This is consistent with the observation that adjudicated attacks in inebilizumab-treated participants had a lower optico-spinal impairment score (OSIS) than those receiving placebo.
- sGFAP concentrations decreased in inebilizumab-treated patients who did not experience an adjudicated NMOSD attack.
- These observations suggest that sGFAP could be a clinically useful biomarker of disease activity and increased attack risk in NMOSD.

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